SYNTHESIS OF DERIVATIVES OF 3,5-DIOXOPYRAZOLIDINE

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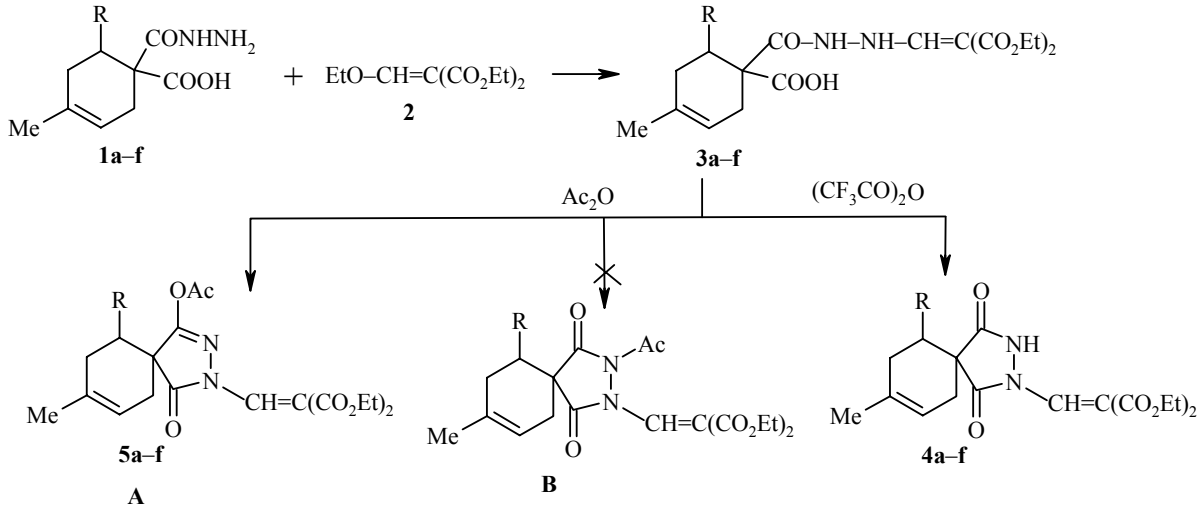
The reaction of monohydrazides of 2-R-4-methylcyclohex-4-ene-1,1-dicarboxylic acids with ethoxymethylenemalonic acid diethyl ester leads to N-(2,2-diethoxycarbonylethylenyl)hydrazides of 2-R-4-methylcyclohex-4-ene-1,1-dicarboxylic acids, which are acylated by the anhydrides of trifluoroacetic and acetic acids with the formation of derivatives of 3,5-dioxopyrazolidine and 5-oxopyrazoline respectively.

Keywords: hydrazides of cyclohexenedicarboxylic acids, 3,5-dioxopyrazolidines, diethyl ester of ethoxymethylenemalonic acid, 5-oxopyrazolines.

We established previously [1] that the interaction of monohydrazides of 2-R-4-methylcyclohex-4-ene-1,1-dicarboxylic acids with acid anhydrides leads to the formation of 4,4-spiro-substituted 3,5-dioxopyrazolidines.

The present work is devoted to the study of the possibility of synthesizing derivatives of 3,5-dioxopyrazolidine under analogous conditions from N-substituted monohydrazides. To obtain the latter the reaction of hydrazides **1a-f** with the diethyl ester of ethoxymethylenemalonic acid (**2**) was carried out. As in the condensation of ester **2** with arylhydrazines, the reaction of compound **2** with hydrazines **1a-f** occurs exclusively at the enolic ethoxy group of diethyl ethoxymethylenemalonate **2** with the formation of N-(2,2-diethoxycarbonylethylenyl)hydrazides of 2-R-4-methylcyclohex-4-ene-1,1-dicarboxylic acids **3a-f**.



1, **3-5 a** R = H, **b** R = Ph, **c** R = 4-FC_6H_4, **d** R = 4-ClC_6H_4, **e** R = 4-BrC_6H_4, **f** R = 4-$O_2NC_6H_4$

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TABLE 1. Characteristics of the Synthesized Compounds **3-5**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Hal		
3a	$C_{17}H_{24}N_2O_7$	55.48 / 55.43	6.25 / 6.57	7.52 / 7.60		162-164	91.4
3b	$C_{23}H_{28}N_2O_7$	62.05 / 62.14	6.29 / 6.36	6.18 / 6.30		168-169	78.9
3c	$C_{23}H_{27}FN_2O_7$	59.83 / 59.76	6.02 / 5.89	6.12 / 6.06	4.14 / 4.11	174-176	75.4
3d	$C_{23}H_{27}ClN_2O_7$	57.46 / 57.68	5.74 / 5.68	5.58 / 5.85	7.35 / 7.40	132-134	95.1
3e	$C_{23}H_{27}BrN_2O_7$	52.71 / 52.78	5.06 / 5.20	5.50 / 5.35	15.53 / 15.27	137-139	97.9
3f	$C_{23}H_{27}N_3O_9$	56.46 / 56.44	5.54 / 5.56	8.32 / 8.58		184-186	80.6
4a	$C_{17}H_{22}N_2O_6$	58.97 / 58.27	6.32 / 6.33	7.87 / 7.99		153-154	62.9
4b	$C_{23}H_{26}N_2O_6$	64.55 / 64.77	5.58 / 6.14	6.76 / 6.57		131-132	65.1
4c	$C_{23}H_{25}FN_2O_6$	62.28 / 62.16	5.80 / 5.67	6.34 / 6.30	4.08 / 4.27	114-116	68.4
4d	$C_{23}H_{25}ClN_2O_6$	60.06 / 59.94	5.35 / 5.47	6.18 / 6.08	7.71 / 7.70	138-140	78.9
4e	$C_{23}H_{25}BrN_2O_6$	54.72 / 54.66	4.89 / 4.99	5.70 / 5.54	15.99 / 15.81	140-142	78.5
4f	$C_{23}H_{25}N_3O_8$	58.42 / 58.59	5.62 / 5.35	8.93 / 8.91		124-125	73.7
5a	$C_{19}H_{24}N_2O_7$	58.13 / 58.15	6.25 / 6.16	7.25 / 7.14		132-133	64.1
5b	$C_{25}H_{28}N_2O_7$	63.82 / 64.08	5.92 / 6.04	6.13 / 5.98		102-103	61.7
5c	$C_{25}H_{27}FN_2O_7$	61.83 / 61.72	5.61 / 5.59	5.83 / 5.76	3.90 / 3.91	134-136	81.1
5d	$C_{25}H_{27}ClN_2O_7$	59.95 / 59.69	5.38 / 5.41	5.36 / 5.57	7.12 / 7.05	142-143	70.0
5e	$C_{25}H_{27}BrN_2O_7$	54.72 / 54.85	4.91 / 4.97	5.15 / 5.12	14.63 / 14.60	132-134	71.8
5f	$C_{25}H_{27}N_3O_9$	58.52 / 58.48	5.35 / 5.30	8.21 / 8.18		183-185	85.7

On brief boiling of N-substituted hydrazides **3a-f** with trifluoroacetic anhydride diethyl (8-methyl-1,4-dioxo-6-R-2,3-diazaspiro[4,5]dec-8-en-2-yl)malonates **4a-f** are formed. Their structures were established on the basis of ^{1}H NMR spectra and their composition was confirmed by data of elemental analysis. In the ^{1}H NMR spectra of compounds **4a-f** only one broadened signal was observed at low field for the NH proton at 9.02-10.07 ppm. The characteristic absorption of the *trans*-fixed fragment =CH–NH– as two doublets ($\delta_{=CH}$ 7.49-7.98, δ_{NH} 9.98-10.23 ppm) and the broadened low-field signal of the carboxyl group protons, recorded in the ^{1}H NMR spectra of compounds **3a-f**, were absent.

Reaction of hydrazides **3a-f** with acetic anhydride occurs on boiling the initial products for 1 h and leads to the formation of analogous cyclic but already acetylated products. The presence in the molecule of 3,5-dioxopyrazolidine of two nucleophilic centers affords the possibility of forming products of both O-acylation (**A**) and also N-acylation (**B**). It is not possible to form an opinion on the site of acylation from data of ^{1}H NMR spectra and elemental analysis. The choice in favor of the O-acyl product was made by us on the basis of the results of [1] and on the data of IR spectra, in which high frequency absorption bands were observed for the ester carbonyl of an acetoxy group at 1700-1716 cm^{-1} and there was no absorption for amide carbonyl and NH groups.

TABLE 2. Spectral Characteristics of the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}		^1H NMR spectrum, δ, ppm (SSCC, *J*, Hz)*
	C=O	NH	
1	2	3	4
3a	1740, 1700, 1680, 1640	3315-3215	1.21 (3H, t, *J* = 7, CH_3); 1.25 (3H, t, *J* = 7, CH_3); 1.66 (3H, s, CH_3); 1.97-2.20 (4H, m, $2CH_2$); 2.58 (2H, m, 2CH); 4.21 (4H, m, $2CH_2$); 5.42 (1H, m, =CH–); 7.98 (1H, d, *J* = 12.5, =CH–); 9.48 (1H, br. s, NH); 10.16 (1H, d, *J* = 12.5, NH); 11.20 (1H, br. s, COOH)
3b	1748, 1700, 1690, 1650	3300-3200	1.22 (3H, t, *J* = 7, CH_3); 1.25 (3H, t, *J* = 7, CH_3); 1.67 (3H, s, CH_3); 2.28-2.89 (4H, m, $2CH_2$); 3.61 (1H, m, CH); 4.07 (4H, q, *J* = 7, $2CH_2$); 5.44 (1H, m, =CH–); 7.16 (5H, m, Ar); 7.69 (1H, d, *J* = 13, =CH); 9.13 (1H, br. s, NH); 9.29 (1H, br. s, COOH); 9.93 (1H, d, *J* = 13, NH)
3c	1742, 1702, 1675, 1617	3330-3220	1.22 (3H, t, *J* = 7, CH_3); 1.25 (3H, t, *J* = 7, CH_3); 1.71 (3H, s, CH_3); 2.26-2.82 (4H, m, $2CH_2$); 2.65 (1H, m, CH); 4.13 (4H, q, *J* = 7, $2CH_2$); 5.49 (1H, m, =CH–); 6.78-7.24 (4H, m, Ar); 7.73 (1H, d, *J* = 13, =CH); 9.29 (1H, br. s, NH); 9.93 (1H, d, *J* = 13, NH); 10.31 (1H, br. s, COOH)
3d	1738, 1700, 1670, 1615	3328-3220	1.23 (3H, t, *J* = 7, CH_3); 1.25 (3H, t, *J* = 7, CH_3); 1.69 (1H, s, CH_3); 2.19-2.93 (4H, m, $2CH_2$); 3.63 (1H, m, CH); 4.15 (4H, q, *J* = 7, $2CH_2$); 5.51 (1H, m, =CH); 7.26 (4H, m, Ar); 7.76 (1H, d, *J* = 14, =CH–); 9.15 (1H, br. s, NH); 9.87 (1H, d, *J* = 14, NH); 9.92 (1H, br. s, COOH)
3e	1734, 1702, 1670, 1620	3350-3220	1.21 (3H, t, *J* = 7, CH_3); 1.23 (3H, t, *J* = 7, CH_3); 1.62 (3H, s, CH_3); 1.84-2.91 (4H, m, $2CH_2$); 3.78 (1H, m, CH); 4.12 (4H, q, *J* = 7, $2CH_2$); 5.49 (1H, m, =CH); 7.16 (2H, m, *J* = 8, Ar); 7.44 (2H, m, *J* = 8, Ar); 7.69 (1H, d, *J* = 14, =CH–); 10.29 (1H, d, *J* = 14, NH); 11.10 (1H, br. s, NH); 11.50 (1H, br. s, COOH)
3f	1730, 1715, 1680, 1615	3400-3310	1.21 (3H, t, *J* = 7, CH_3); 1.23 (3H, t, *J* = 7, CH_3); 1.71 (3H, s, CH_3); 1.92-2.93 (4H, m, $2CH_2$); 4.05 (1H, m, CH); 4.13 (4H, q, *J* = 7, $2CH_2$); 5.59 (1H, m, CH); 7.49 (2H, m, *J* = 8, Ar); 7.69 (1H, d, *J* = 13, =CH–); 8.15 (2H, m, *J* = 8, Ar); 10.25 (1H, d, *J* = 13, NH); 10.96 (1H, br. s, NH); 11.10 (1H, br. s, COOH)
4a	1740, 1720, 1680, 1610	3100	1.29 (3H, t, *J* = 7, CH_3); 1.32 (3H, t, *J* = 7, CH_3); 1.69 (3H, s, CH_3); 1.89-2.33 (6H, m, $3CH_2$); 4.24 (2H, q, *J* = 7, CH_2); 4.31 (2H, q, *J* = 7, CH_2); 5.38 (1H, m, =CH–); 8.08 (1H, s, =CH–); 10.07 (1H, br. s, NH)
4b	1745, 1730, 1680, 1610	3220	1.21 (6H, m, $2CH_3$); 1.71 (3H, s, CH_3); 1.92-3.38 (5H, m, $2CH_2$, CH); 4.26 (4H, m, $2CH_2$); 5.43 (1H, m, CH); 7.16 (5H, m, C_6H_5); 7.96 (1H, s, =CH–); 9.78 (1H, br. s, NH)
4c	1740, 1720, 1680, 1610	3210	1.25 (3H, t, *J* = 7, CH_3); 1.28 (3H, t, *J* = 7, CH_3); 1.76 (3H, s, CH_3); 2.02–2.99 (4H, m, $2CH_2$); 3.33 (1H, m, CH); 4.18 (4H, q, *J* = 7, $2CH_2$); 5.38 (1H, m, =CH–); 6.89-7.11 (4H, m, Ar); 7.96 (1H, s, =CH–); 9.60 (1H, br. s, NH)
4d	1740, 1725, 1685, 1620	3230	1.29 (3H, t, *J* = 7, CH_3); 1.31 (3H, t, *J* = 7, CH_3); 1.82 (3H, s, CH_3); 2.09-3.39 (5H, m, CH); 3.39 (5H, m, $2CH_2$, CH); 4.21 (4H, q, *J* = 7, $2CH_2$); 5.42 (1H, m, =CH–); 7.05-7.21 (4H, m, Ar); 9.02 (1H, s, =CH–); 9.02 (1H, br. s, NH)
4e	1745, 1720, 1682, 1615	3210	1.22 (3H, t, *J* = 7, CH_3); 1.25 (3H, t, *J* = 7, CH_3); 1.73 (3H, s, CH_3); 1.97–3.01 (4H, m, $2CH_2$); 3.36 (1H, m, CH); 4.19 (4H, q, *J* = 7, $2CH_2$); 5.39 (1H, m, =CH–); 7.05-7.42 (4H, m, Ar); 8.02 (1H, s, =CH–); 9.36 (1H, br. s, NH)
4f	1740, 1716, 1680, 1610	3200	1.25 (6H, m, $2CH_3$); 1.78 (3H, s, CH_3); 2.09-3.09 (4H, m, $2CH_2$); 3.53 (1H, m, CH); 4.21 (4H, m, $2CH_2$); 5.49 (1H, m, CH); 7.31 (2H, m, Ar); 8.11 (3H, m, Ar, =CH–); 9.97 (1H, br. s, NH)

TABLE 2 (continued)

1	2	3	4
5a	1760, 1732, 1700, 1630		1.22 (6H, t, *J* = 7, $2CH_3$); 1.66 (3H, s, CH_3); 1.86-2.38 (6H, m, $3CH_2$); 2.53 (3H, s, CH_3); 4.11 (4H, q, *J* = 7, $2CH_2$); 5.28 (1H, m, =CH–); 7.44 (1H, s, =CH–)
5b	1770, 1745, 1715, 1645		1.27 (6H, t, *J* = 7, CH_3); 1.29 (3H, t, *J* = 7, CH_3); 1.76 (3H, s, CH_3); 2.04 (3H, s, CH_3); 2.11-3.01 (4H, m, $2CH_2$); 3.22 (1H, m, CH); 4.22 (2H, q, *J* = 7, CH_2); 4.25 (2H, q, *J* = 7, CH_2); 5.38 (1H, m, =CH–); 7.21 (1H, s, =CH–); 7.25 (5H, m, Ar)
5c	1760, 1740, 1716, 1640		1.22 (3H, t, *J* = 7, CH_3); 1.25 (3H, t, *J* = 7, CH_3); 1.73 (3H, s, CH_3); 2.13 (3H, s, CH_3); 2.07-3.02 (4H, m, $2CH_2$); 3.24 (1H, m, CH); 4.18 (2H, q, *J* = 7, CH_2); 4.23 (2H, q, *J* = 7, CH_2); 5.37 (1H, m, =CH–); 7.04 (4H, m, Ar); 7.07 (1H, m, =CH–)
5d	1765, 1740, 1715, 1640		1.27 (6H, t, *J* = 7, CH_3); 1.29 (3H, t, *J* = 7, CH_3); 1.73 (3H, s, CH_3); 2.02-2.89 (4H, m, $2CH_2$); 2.17 (3H, s, CH_3); 3.22 (1H, m, CH); 4.18 (4H, m, $2CH_2$); 5.41 (1H, m, =CH–); 7.16 (1H, s, =CH–); 7.21 (4H, m, Ar)
5e	1760, 1740, 1715, 1640		1.24 (3H, t, *J* = 7, CH_3); 1.27 (3H, t, *J* = 7, CH_3); 1.71 (3H, s, CH_3); 2.07-2.93 (4H, m, $2CH_2$); 3.21 (1H, m, CH); 4.18 (4H, m, $2CH_2$); 5.28 (1H, m, =CH–); 7.11 (2H, m, *J* = 8, Ar); 7.11-7.38 (5H, m, Ar, =CH–)
5f	1765, 1730, 1716, 1640		1.26 (3H, t, *J* = 7, CH_3); 1.28 (3H, t, *J* = 7, CH_3); 1.73 (3H, s, CH_3); 2,16 (3H, s, CH_3); 2.02-3.07 (4H, m, $2CH_2$); 3.42 (1H, m, CH); 4.18 (2H, q, *J* = 7, CH_2); 4.21 (2H, q, *J* = 7, CH_2); 5.38 (1H, m, =CH–); 7.29 (2H, m, *J* = 8, Ar); 7.32 (1H, s, =CH); 8.16 (2H, m, *J* = 8, Ar)

* Compounds **3c,f** in DMSO-d_6, remainder in $CDCl_3$.

EXPERIMENTAL

The ^1H NMR spectra were obtained on a WH 90/DS (90 MHz) instrument, solvents were $CDCl_3$ and DMSO-d_6, internal standard was HMDS (0.055 ppm). The IR spectra were recorded on a Specord 75 instrument for suspensions in nujol and hexafluorobutadiene. The homogeneity of the compounds obtained was checked by TLC on Silufol plates in the solvent system chloroform–methanol–acetic acid, 95:5:5.

Monohydrazides **1a-f** were synthesized by us previously in [3]. The diethyl ester of ethoxymethylenemalonic acid (**2**) was given by BAPEKS.

N-(2,2-Diethoxycarbonylethylenyl)hydrazides of 2-R-4-Methylcyclohex-4-ene-1,1-dicarboxylic Acids (3a-f). A suspension of hydrazide **1a-f** (5 mmol) and an equimolar quantity of diethyl ester **2** in ethanol (40 ml) was boiled for 1 h. Half of the ethanol was distilled off, water (~10 ml) was added to the residue, and the mixture left for 10-12 h. The mixture was filtered, and the product recrystallized for analysis from ethanol.

Diethyl (8-Methyl-1,4-dioxo-6-R-2,3-diazaspiro[4,5]dec-8-en-2-yl)methylenemalonate (4a-f). Hydrazide **3a-f** (1 mmol) was boiled in trifluoroacetic anhydride (1.5 ml) for 1 h. The trifluoroacetic anhydride was distilled off, and the residue rubbed with hexane. The mixture was filtered, and the solid recrystallized from ethanol–water, 1:1.

Diethyl (4-Acetoxy-8-methyl-1-oxo-6-R-2,3-diazaspiro[4,5]deca-3,7-dion-2-yl)methylenemalonate (5a-f). Hydrazide **3a-f** (1 mmol) was boiled in acetic anhydride (1.5 ml) for 1 h. The acetic anhydride was distilled off, water (~10 ml) was added to the residue, and the mixture stirred for 1 h. The aqueous solution was decanted, and the solidified oil was recrystallized from ethanol.

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